In the Official Action, the Examiner has suggested that a Declaration be submitted to supplement Applicants' remarks in their Reply to the prior Official Action traversing the rejection under the first paragraph of 35 U.S.C. §112. While it is believed that the specification as filed and the comments submitted in the paper filed January 20, 2000 should be sufficient to overcome the Examiner's objections, Applicants provide herewith an unexecuted copy of a Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez, a Research Director in the organization of the Assignee of the subject application, as suggested by the Examiner. An executed copy of the Declaration will be provided to the Examiner in due course.

In his Declaration, Dr. Demarchez discusses data obtained in experiments conducted by the Applicants as well as statements based on his knowledge of the state of the art. In particular, the Declaration supports the conclusion that several compounds according to the invention have been demonstrated to have biological activity as RAR type agonists, RXR agonists or both (i.e, paragonist compounds). The Declaration also provides a discussion of published references that document the well known scientific finding that retinoids have established utility as therapeutic agents. A copy of the documents referred to in the Declaration in this regard is provided herewith for the Examiner's convenience. As well, the Declaration provides the results of *in vivo* assay tests showing how a compound according to the invention has biological activity in ear oedema.

As discussed by Dr. Demarchez in the Declaration, the fact that the compounds according to the invention comprise therapeutic utility is further substantiated by data which has been obtained by the present inventors relating to several compounds according to the

invention. Specifically, in a biological test, i.e., the F9 test which is an accepted assay for identifying RAR-type agonists, the present inventors have demonstrated that the compounds of Example 2 and Example 6 are RAR-type agonists (see the data presented in Table 1 in the Declaration). Moreover, in another accepted assay, described in Levin et al, *Nature*, Vol. 355, pp. 359-361 (1992), and in Allenby et al, *Proc. Natl. Acad. Sci. USA*, Vol. 90, pp. 30-34 (1993), the inventors confirmed that the compounds of Example 2 and Example 4 function as RXR agonists (see the data presented in Table 2 in the Declaration). As discussed above, and as established by the references attached to this Reply, it is known in the art that such agonists find accepted usage as pharmacological agents, in particular for treatment of disorders involving cell proliferation and differentiation and in particular keratinization related disorders.

In particular, the Examiner is respectfully referred to Safonova et al, *Biochemical and Biophysical Research Communications*, Vol. 204, No. 2, 1994, which discloses the usage of such agonists on cell differentiation and potential therapeutic utility. Moreover, Hong et al, *Retinoids and Human Cancer*, from *The Retinoids: Biology, Chemistry, and Medicine*, 2nd Ed., 1994, reviews the accepted usage of retinoids in the treatment of human cancer. The reference identifies numerous retinoids having such utility including all-trans retinoic acid, isotretoin, etretinate, fenretinide, and arotinoids. Also, as summarized in Dr. Demarchez's Declaration, Lippman and DiGiovanna, *Retinoids and Skin Cancer*, teaches the potential usage of retinoids in treating such disorder and the use of single agent retinoid therapies in advanced malignant disease such as acute promyelocytic leukemia, mycosis

fungoides, and skin cancer. The authors indicate that retinoids show great therapeutic promise in such treatments.

Also, as discussed in the Declaration, Kavanagh et al, *Retinoids and Cervical Cancer*, disclose that topical trans-retinoic acid is active in the treatment of cervical carcinogenesis with complete lesion reversal obtained in one trial.

In particular, the Examiner is referred to Table 2, which summarizes the results of studies of local retinoid activity and toxicity in the treatment of cervical displasia. Still further, Meyskens et al, *Role of topical tretinoin in melanoma and dysplastic nevi*, Vol. 15, No. 4 (1986), discloses the usage of topical tretinoin in the treatment of melanoma and dysplastic nevi, with the authors concluding that such administration had activity against melanoma, and its precursor conditions.

Therefore, based on the foregoing, Applicants respectfully submit that the efficacy of retinoid compounds as pharmaceutical agents is accepted in the art. Therefore, based on the data provided in the Declaration demonstrating that compounds according to the invention function as RAR and RXR agonists, it is reasonable to conclude that they will exhibit desirable pharmacological properties and useful in the treatment of the recited conditions. Also, the retinoic acid of compounds according to the invention has further been demonstrated in an *in vivo* assay which measures the effect of compounds according to the invention on ear edema induced by topical administration of a compound according to the invention, specifically the compound of Example 2 (see the data of Table 3 in the Declaration). These results, which are summarized in Dr. Demarchez's Declaration further support that the retinoic acid of Example 2 when applied topically induces an augmentation

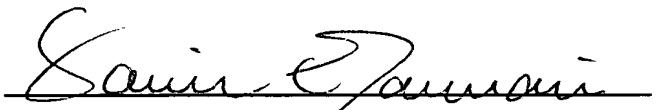
of the ear oedma. This provides further evidence that compounds according to the invention, and specifically the elected compound, may be used in treatment of the recited conditions, in particular treatment of dermatological conditions such as those associated with differentiation and proliferation.

Therefore, based on the foregoing, withdrawal of the §112 enablement rejection of Claims 28-30, 34-36, and 38-41 is respectfully requested. In view of the Declaration provided pursuant to the Examiner's suggestion, it is believed that the enablement rejection has been obviated and should be withdrawn.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 
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